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Vasopressin and its analogues in patients with septic shock: holy Grail or unfulfilled promise?

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Abstract

The Surviving Sepsis Campaign (SSC) recommends norepinephrine as first-line vasopressor in patients with septic shock. For many years, there has been growing evidence that high doses of norepinephrine might have cardiac and immunological adverse effects and be associated with poorer outcomes. Current SSC guidelines therefore suggest adding vasopressin, a non-catecholaminergic vasopressor, as a second-line vasopressor rather than increasing the norepinephrine dose in patients requiring doses of norepinephrine base > 0.25–0.50 µg/kg/min, after excluding persistent hypovolemia and cardiac dysfunction. Vasopressin is a peptide hormone that causes vasoconstriction through its specific receptor, the arginine vasopressin receptor V1. Up to one-third of patients with septic shock may have vasopressin deficiency, which contributes to refractory septic shock. Vasopressin use is associated with a norepinephrine-sparing effect, which may in turn reduce the complications induced by high-doses of norepinephrine, by decreasing the vasopressor load: this is the concept of decatecholaminization. Nevertheless, the use of vasopressin in patients with septic shock has not yet demonstrated clear benefits in terms of patient outcomes, such as less cardiotoxicity, reduced use of renal replacement therapy or decreased mortality. The heterogeneity in the use of vasopressin and the definition of early vasopressin administration between different studies as well as many unresolved issues regarding the use of vasopressin in patients with septic shock could explain the absence of clear and relevant clinical benefits. Thus, the identification of subgroups of patients likely to benefit the most from vasopressin, the management of vasopressin administration (time to initiation, optimal doses, weaning strategy) and a better understanding of the interactions between vasopressin and corticosteroids represent major areas of research for future studies.

Keywords Vasopressin, Antidiuretic hormone, Septic shock, Refractory septic shock, Vasopressors, Norepinephrine, Decatecholaminization

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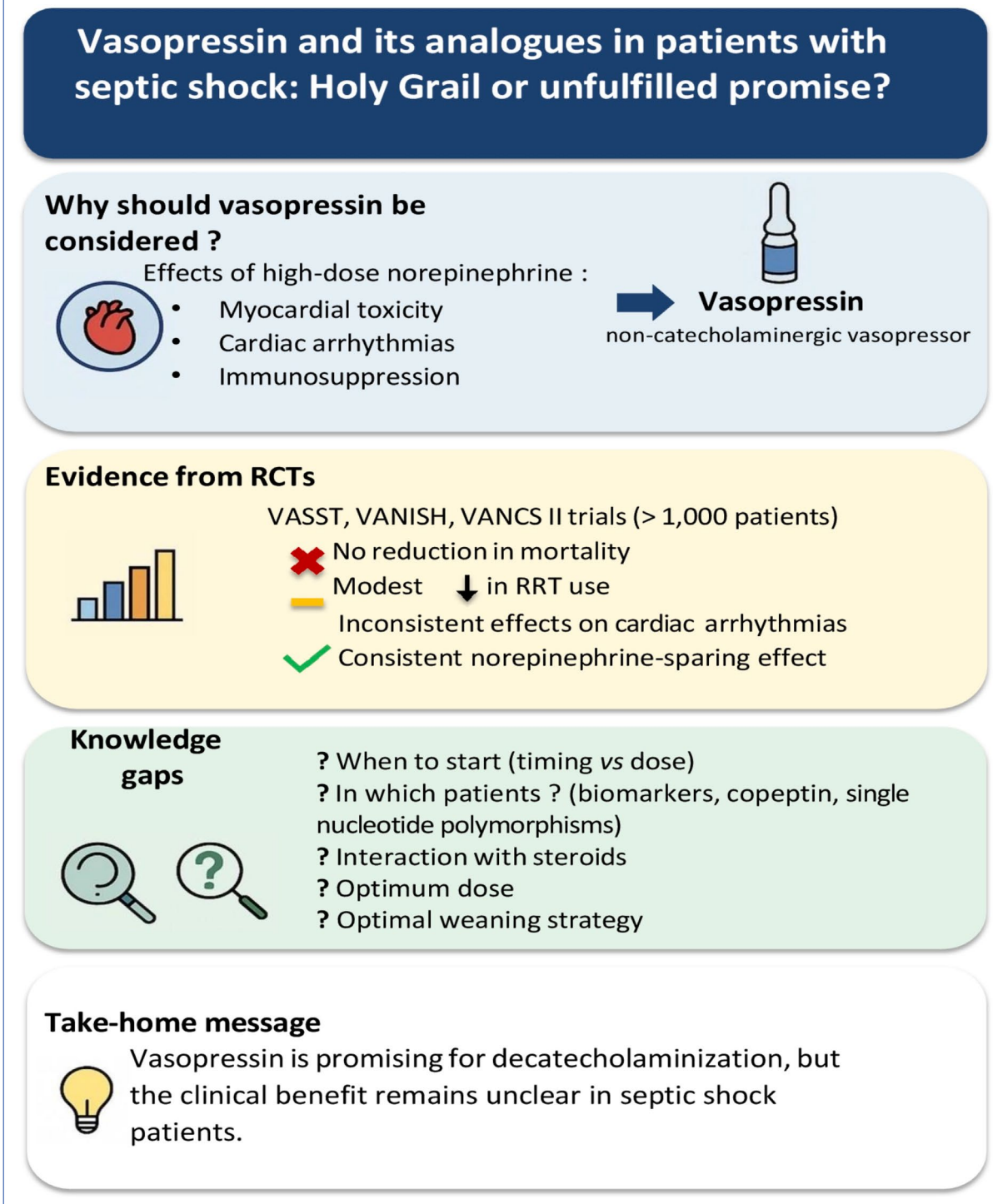
Vasopressin and its analogues in patients with septic shock: Holy Grail or unfulfilled promise?
Why should vasopressin be considered ?
Effects of high-dose norepinephrine :
Myocardial toxicity
Cardiac arrhythmias
Immunosuppression
Vasopressin
non-catecholaminergic vasopressor
Evidence from RCTs
VASST, VANISH, VANCS II trials (> 1,000 patients)
No reduction in mortality
Modest in RRT use
Inconsistent effects on cardiac arrhythmias
Consistent norepinephrine-sparing effect
Knowledge gaps
? When to start (timing vs dose)
? In which patients ? (biomarkers, copeptin, single nucleotide polymorphisms)
? Interaction with steroids
? Optimum dose
? Optimal weaning strategy
Take-home message
Vasopressin is promising for decatecholaminization, but the clinical benefit remains unclear in septic shock patients.

Introduction

Sepsis accounts for approximately 7% of adult hospital admissions in France, with an incidence of 243 per 100,000 inhabitants [1], and is responsible for more deaths than acquired immunodeficiency syndrome, prostate cancer, and breast cancer altogether in the US [2]. Septic shock accounts for 6.8% of intensive care unit (ICU) admissions in France, with mortality rate of 45% [3], which is consistent with European and North American data, where septic shock accounts for 10.4% of ICU admissions, has an incidence of 8% during ICU stay, and results in a 28-day mortality of around 37% [4].

According to the Surviving Sepsis Campaign (SSC), the treatment of septic shock is based on controlling the source of infection, antimicrobial therapy and hemodynamic management combining the administration of fluids and vasopressors, with norepinephrine being the recommended first-line vasopressor [5]. Norepinephrine sparing could potentially reduce mortality in patients with septic shock, as higher doses of norepinephrine are associated with a higher mortality rate [6, 7]. Norepinephrine may have significant adverse effects, such as increased myocardial oxygen consumption, cardiac arrhythmias [8, 9], direct toxicity to cardiomyocytes [10] and immunosuppression [11, 12]. In this regard, the SSC guidelines suggest adding vasopressin, as a second-line vasopressor, rather than increasing the norepinephrine dose in patients requiring doses of norepinephrine base > 0.25–0.50 µg/kg/min [5]. Two international surveys indicate a general adherence to these guidelines, with around 80% of intensivists stating that they would consider vasopressin or analogues as second-line vasopressor in patients with refractory arterial hypotension despite adequate initial hemodynamic management [13, 14]. However, there is substantial heterogeneity across different regions of the world [15].

Consequently, the use of vasopressin is increasing despite its high cost [16]. Previous reviews have focused on the physiological effects of vasopressin on various organ systems [17], the pathophysiology of shock [18], the use of different vasopressors during septic shock [19, 20], or the administration of vasopressin in other shock states [21]. However, while vasopressin has demonstrated physiological benefits, such as improving hemodynamics and sparing catecholamine, evidence of its impact on patient-centered outcomes in septic shock, including mortality, remains inconclusive. Challenges such as heterogeneity in the time to vasopressin initiation and patient selection may explain these limitations.

This narrative review will focus on the potential benefits of vasopressin and its analogues in patients with septic shock, highlighting the current knowledge, identifying gaps in knowledge, and proposing future areas of research.

Concept of decatecholaminization

Norepinephrine is currently recommended as first-line vasopressor in patients with septic shock [5], since norepinephrine induces fewer cardiac arrhythmias than dopamine and epinephrine [19, 22] and lower myocardial oxygen consumption and less increase in heart rate than epinephrine [23]. Its effects on macro- and microcirculation are related to the activation of its α- and β1-adrenergic receptor [24]. At the macrocirculatory level, norepinephrine increases the venous return [25, 26] by increasing the mean systemic filling pressure and therefore the pressure gradient of venous return [27, 28]. Norepinephrine also increases arterial pressures, including the mean arterial pressure (MAP), and improves the coronary perfusion because of the increase in diastolic arterial pressure and its coronary vasodilatory effect by releasing endothelium-derived relaxing factors [29]. Additionally, norepinephrine increases stroke volume and therefore cardiac output without inducing tachycardia, irrespective of the left ventricular ejection fraction of the patients [25, 30]. This effect is related to the increase in intrinsic inotropic property on the myocardium [23, 30]. Norepinephrine thus improves ventriculo-arterial coupling and load-independent measurements of cardiac systolic function [24]. At the microcirculatory level, the increase in MAP level by increasing the norepinephrine dose is associated with an improvement of sublingual microcirculation [31, 32]. Moreover, early correction of arterial hypotension with norepinephrine improved tissue oxygenation and microcirculatory reserve capacities, that can be explained by the reopening of pressure-dependent vascular beds [33]. Norepinephrine is therefore considered an "inopressor" combining both vasopressor and inotropic effects [34].

However, norepinephrine may have adverse effects that can affect patients' prognosis. First, norepinephrine dose ≥ 0.75 µg/kg/min is closely associated with patient prognosis [35], especially within the first 24 h of septic shock [36]. For the same MAP range [37] and patient severity [35], higher norepinephrine doses are associated with a higher mortality rate. Second, in patients with septic shock, there is a down-regulation of adrenergic receptors [38], reducing the efficiency of norepinephrine administration. Third, high norepinephrine doses may induce a left ventricular outflow tract obstruction in patients with myocardial hypertrophy [39]. Fourth, norepinephrine also has direct myocardial toxicity *via* different mechanisms (cAMP-mediated calcium overload, formation of oxygen-derived free radicals, etc.) [10] leading to myocardial inflammation and necrosis [40], and its β1-adrenergic effects can lead to ventricular and supraventricular cardiac arrhythmias, including cardiac arrest due to ventricular fibrillation [9]. Finally, norepinephrine might also exhibit immunomodulatory properties with a

decrease in pro-inflammatory cytokines (tumor necrosis factor-α, interleukin-1 interleukin-β, interleukin-6), an increase in anti-inflammatory cytokines (interleukin-10), a Th1 to Th2 switch in T cells and reduced NK cells cytotoxicity). Furthermore, norepinephrine exposure enhances *Staphylococcus sp.* growth and biofilm production in vitro, even if in vivo data are lacking [12]. The effects of norepinephrine and vasopressin on the immune response and host defense have been compared in mice and healthy volunteers [41]. In the murine model, norepinephrine promoted peripheral bacterial dissemination, whereas vasopressin did not. In LPS-challenged volunteers norepinephrine dysregulated the immune response and compromised host defense through its β_2-adrenergic effects, while vasopressin did not alter cytokine concentrations [41]. Altogether, these data suggest that norepinephrine might contribute to the sepsis-induced immunoparalysis.

There is therefore a growing interest in using non-catecholaminergic vasopressors, like vasopressin and angiotensin II [42], to mitigate these adverse effects and improve outcomes [43], leading to the concept of decatecholaminization [44].

Physiological effects of vasopressin

Vasopressin, also known as arginine vasopressin or antidiuretic hormone, is a peptide synthesized by the supraoptic and paraventricular nuclei of the hypothalamus and released by the posterior pituitary gland into the systemic circulation [45] (Fig. 1). Vasopressin is secreted as a preprohormone, which is cleaved into neurophysin II, the nonapeptide arginine vasopressin and copeptin [46]. Physiologically, vasopressin is released in response to an increase in plasma osmolality, detected by hypothalamic osmoreceptors, and/or a decrease in blood volume or blood pressure sensed by baroreceptors in the carotid sinus, left atrium, and pulmonary artery [47].

Vasopressin exerts pleiotropic effects through the activation of different receptors (Fig. 2). The arginine vasopressin receptors 1 (V1) are expressed by liver, kidney, vascular smooth cells, and brain cells [48]. V1 activation leads to increased intra-cytosolic calcium concentrations in an α-adrenergic independent pathway *via* the activation of phospholipase C, which converts phosphatidylinositol-4,5-bisphosphate into diacylglycerol and activates inositol trisphosphate, which in turn triggers the calcium release from the endoplasmic reticulum, promoting myosin-mediated vasoconstriction [49, 50]. Through V1 activation, vasopressin also lowers pulmonary artery pressure [51, 52], enhances renal function by inducing efferent vasoconstriction [18, 53], and regulates the circadian rhythm and olfactory function [48]. Unlike in healthy people, the vasopressor effect of vasopressin is increased in patients with septic shock with predominant V1-mediated effects [54, 55]. The arginine vasopressin receptors 3 (V3) are located in the pituitary gland (anterior and posterior) and pancreas, enabling insulin secretion and the release of adrenocorticotropic hormone [56, 57] (Fig. 1 and Fig. 2). This neurohormonal interaction between vasopressin and corticotropic axis may induce an interaction between vasopressin and steroids, since vasopressin induces adrenal secretion of cortisol and steroids may enhance tissue sensitivity to its vasopressor effects. The arginine vasopressin receptors 2 (V2) are located on renal tubular cells, enabling the insertion of water-permeable aquaporin-2 channels into the cell membrane in renal collecting tubule leading to water reabsorption [58], the release of von Willebrand factors, and the expression of P-selectin, which in turn allows leukocyte adhesion by endothelial cells [59].

Through its combined actions on these receptors, vasopressin contributes to hemodynamic stability, endocrine regulation, and immune modulation, making it a potential therapeutic agent, particularly in conditions such as septic shock.

Is vasopressin really the Holy Grail for patients in septic shock

To date, three large, randomized trials have assessed the effects of vasopressin in patients with septic shock [60–62]. In the first one, the VAAST trial, 778 patients with septic shock (MAP < 65 mmHg receiving > 5 μg/kg/min of norepinephrine) were randomized to receive either norepinephrine alone or norepinephrine plus a low-dose vasopressin (0.01 to 0.03 U/min) [60]. In the second one, the VANISH trial, 421 patients with septic shock were randomized to receive as first-line vasopressor either norepinephrine or vasopressin (titrated on MAP level up to 0.06 U/min). It must be kept in mind that 76% of patients in the vasopressin group already received norepinephrine at the time of inclusion [61]. In the third one, the VANCS II trial, 200 cancer patients with septic shock were randomized to receive as first-line vasopressor either norepinephrine or vasopressin (titrated on MAP level up to 0.06 U/min) [62].

Absence of effect on mortality

None of these trials [60–62] found a difference in 28-day mortality between norepinephrine and vasopressin groups and there was also no difference between groups for 90-day mortality in the VASST trial [60](Table 1). However, the VASST trial may have been underpowered (observed 28-day mortality rate of 35–40% vs. an expected mortality rate of 60%). Moreover, while no survival benefit was demonstrated in the whole population, a trend towards reduced 28-day mortality (26.5% vs. 35.7%, $p = 0.05$) and significantly lower 90-day mortality (35.8% vs. 46.1%, $p = 0.04$) was observed in the less

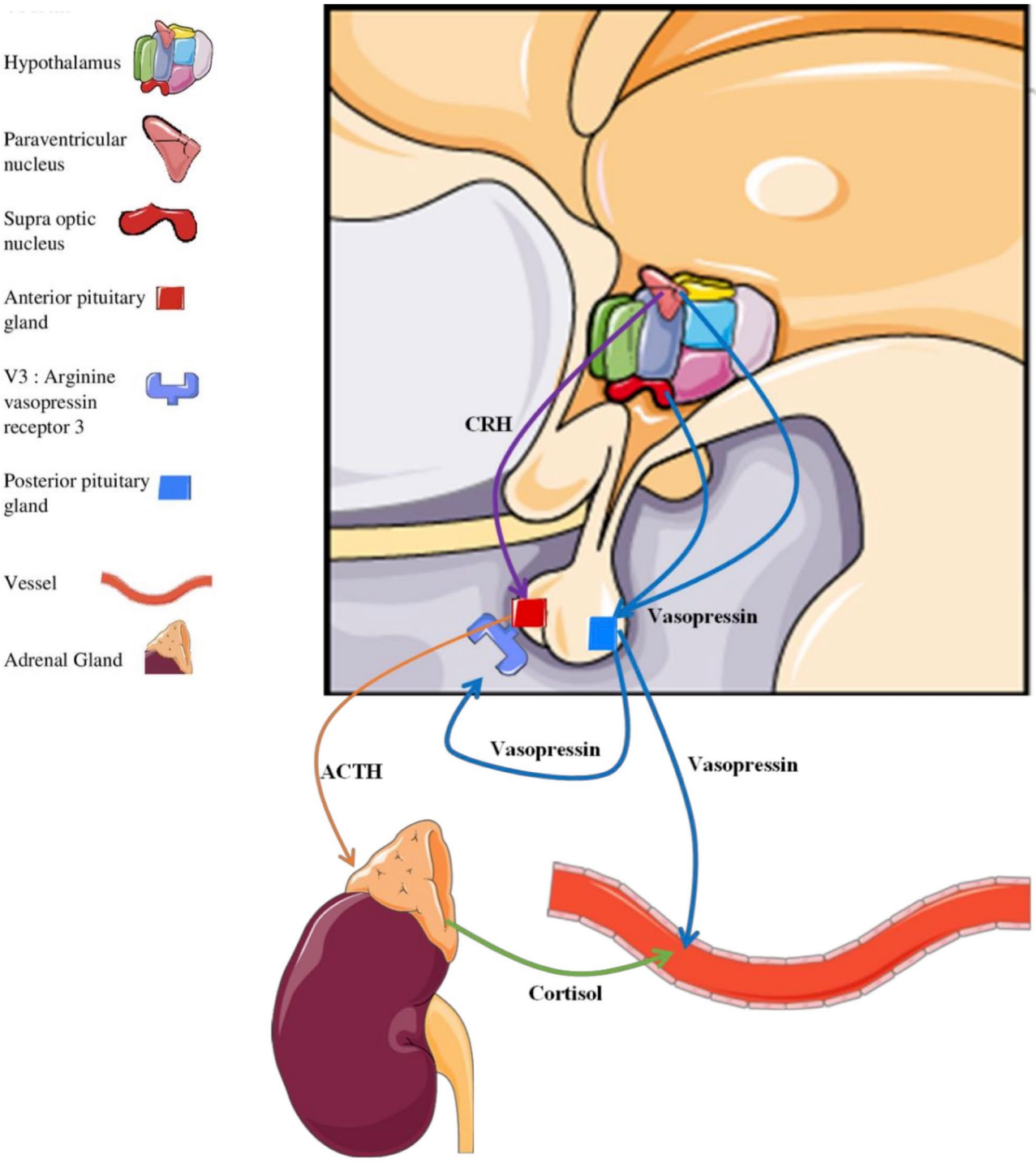

Fig. 1 Neurohormonal interaction between vasopressin and the corticotropic axis. Vasopressin is synthesized in the paraventricular and supraoptic nuclei and released by the posterior pituitary gland into the systemic circulation. By binding to its arginine vasopressin receptor 3 (V3) located in the anterior pituitary gland, vasopressin activates the corticotropic cells, which release the adrenocorticotropic hormone (ACTH), inducing adrenal cortisol secretion into the bloodstream. CRH: Corticotropin-releasing hormone. Figure created with the assistance of Servier Medical Art (https://smart.servier.com), licensed under Creative Commons Attribution 3.0 Unported License

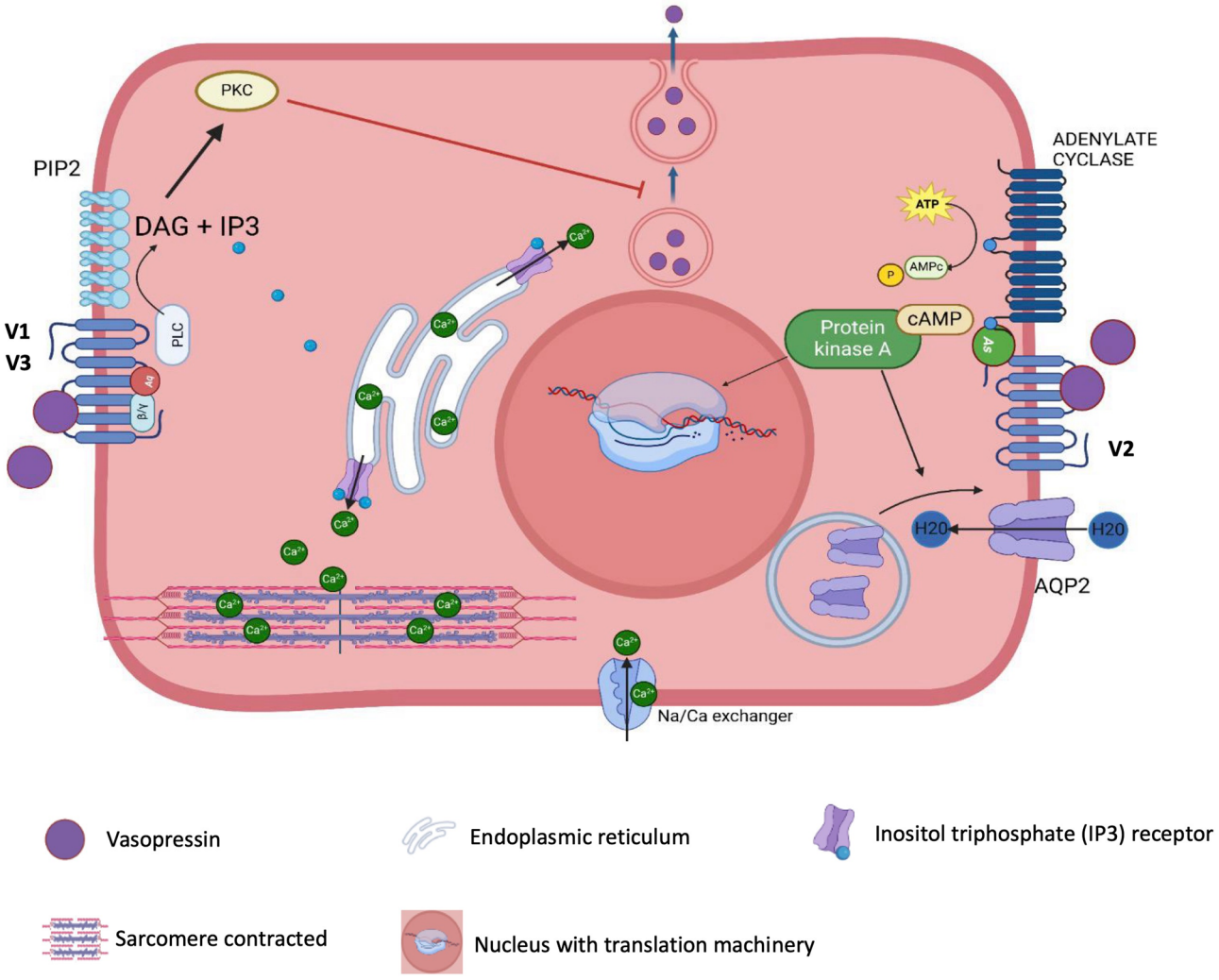

Fig. 2 The different intracellular signalling pathways of vasopressin. For sake of simplicity, a single cell was represented. Figure created with the assistance of BioRender (www.biorender.com). PIP2: phosphatidylinositol biphosphate; DAG: diacylglycerol; IP3: inositol trisphosphate; PKC: protein kinase C; cAMP: cyclic adenosine monophosphate *Arginine vasopressin receptor 1 (V1) pathway*: after binding to V1 located on the surface of vascular smooth cells, vasopressin activates the phospholipase C (PLC) pathway, resulting in the release of calcium (Ca^{2+}) from the endoplasmic reticulum and thus an increase in intracytosolic Ca^{2+} concentration *Arginine vasopressin receptor 2 (V2) pathway*: after binding to V2 located in the renal collecting duct, vasopressin activates a protein kinase A (PKA) pathway, resulting in the translocation of aquaporin-2 (AQP2) to the apical membrane of the cell, facilitating water reabsorption. Activation of the PKA pathway also promotes transcription of the AQP2 gene *Arginine vasopressin receptor 3 (V3) pathway*: after binding to V3 located in the posterior pituitary, vasopressin activates the PLC pathway, leading to inhibition of exocytosis of vasopressin-containing vesicles, thus providing a negative feedback mechanism to regulate hormone release

severe patients, requiring norepinephrine doses < 15 µg/min to maintain MAP > 65 mmHg [60]. Nevertheless, interaction tests between severity of shock and mortality rate did not confirm this potential beneficial effect of vasopressin on mortality [60]. This lack of effect of vasopressin on mortality was subsequently confirmed in two meta-analyses [63, 64] which included only studies with a low risk of bias, regardless of the timing of initiation of vasopressin and including the subgroup with less severe patients.

This lack of effect of vasopressin on mortality could be, at least partly, explained by the adverse effects of vasopressin and especially its ischemic adverse effects. This hypothesis was not confirmed in the VASST, VANISH and VANCS II trial, in which there was no difference between groups in terms of ischemic adverse effects, including mesenteric ischemia, acute coronary syndrome and stroke [60–62]. The fact that unstable coronary patients and those with proven or suspected mesenteric ischemia were excluded probably limited the number of ischemic adverse effects in these trials. However, there was a trend towards an increase in the incidence of digital ischemia with vasopressin in the VASST and VANISH trials [60, 61]. Two meta-analyses found an association

Table 1 Randomized controlled trials assessing the effects of vasopressin on mortality in patients with septic shock

Trial	Design	Sample size	Intervention group	Control group	Primary endpoint	Norepinephrine dose at randomization	Initiation time from diagnosis of septic shock	Use of steroids	Main results on mortality
Malay 1999 [82]	Double Blind Single Center	10	AVP 0.04 U/min	Placebo	Hemodynamic parameters at 24 h	12 µg/min (placebo group) 6.8 µg/min (AVP group)	No data	No	Survival 5/5 in vasopressin group Survival 3/5 in placebo group.
Dünser 2003 [80]	Open Label Single Center	48	AVP 4 U/h	NE 0.5–2.26 µg/kg/min	Hemodynamics between groups during the first 48 h	0.84 µg/kg/min	No data	No data	No difference between groups
VASST 2008 [60]	Double Blind Multicenter	778	AVP 0.01–0.03 U/min with low doses of NE	NE 0.05-2 µg/kg/min	28-day mortality	20.7 µg/min	> 12 h	Yes	No difference between groups Less mortality benefice in less severe patients
Oliveira 2014 [167]	Double Blind Single Center	387	AVP 0.01–0.03 U/min with NE	NE 0.05–2 µg/kg/min	Total time under vasopressors	No data	No data	No data	Decrease in 14 and 28-day mortality
Barzegar 2017 [168]	Open Label Single Center	42	AVP 0.03 U/min with NE	NE (doses not specified)	Sepsis biomarkers (Ang 1 and 2, PTX3, IL-6 and IL-10 and lactate) at 48 h	13.3 µg/min (AVP group) 12.7 µg/min (placebo group)	< 8 h	Yes	No difference between groups
Hammond 2018 [126]	Open Label Single Center	82	NE at 5 µg/min + AVP at 0.04 U/min	NE 15 µg/min	Time to achieve and maintain MAP > 65 mm Hg for 4 h	No data	128 min	Yes	No difference between groups
VANCS II 2019 [62]	Double Blind Single Center	250	AVP 0.01–0.06 U/min	NE 10–60 µg/min	28-day mortality	No data	No data	No data	No difference between groups
VASSPR 2024 [169]	Single Blind Multicenter	2050	NE > 0.1 µg/kg/min + AVP 1.8 U/h	NE > 0.4 µg/kg/min + AVP 1.8U/h	28-day mortality	In progress	< 24 h	Yes	In progress

AVP: Arginine vasopressin; NE: Norepinephrine; U/min: Units per minute; U/h: Units per hour; µg/min: Micrograms per minute; µg/kg/min: Micrograms per kilogram per minute

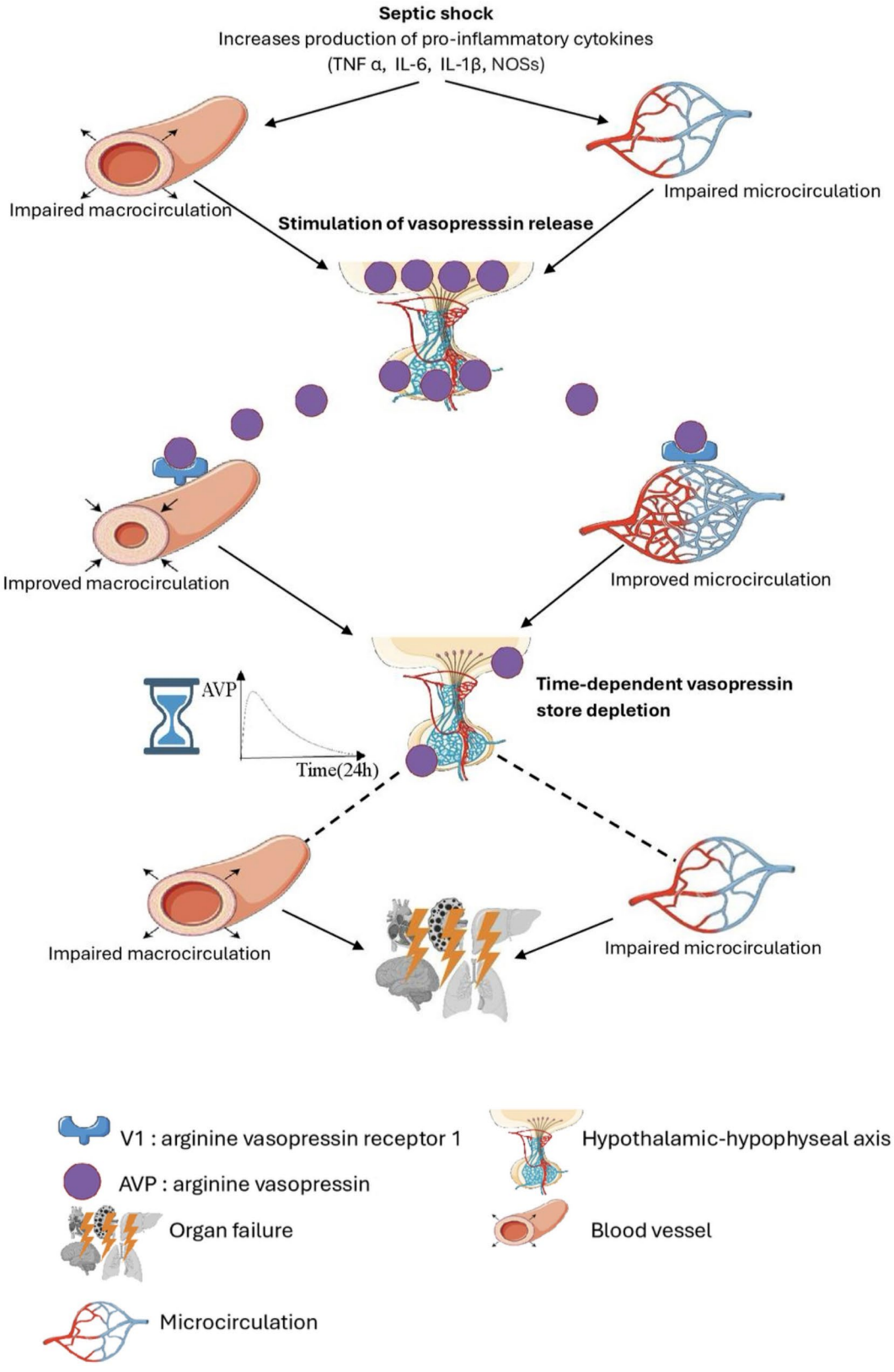

Fig. 3 (See legend on next page.)

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Fig. 3 Vasopressin in patients with septic shock. During sepsis, pro-inflammatory cytokines induce vasodilation, which in turn activates the hypothalamic-pituitary axis to stimulate the release of vasopressin, which binds to its arginine vasopressin receptor 1 (V1) to restore vascular tone. However, this compensatory system is short-lived, as endogenous reserves of vasopressin are rapidly depleted, leading to hypoperfusion and organ dysfunction in absence of treatment. Figure created with the assistance of Servier Medical Art (https://smart.servier.com), licensed under Creative Commons Attribution 3.0 Unported License

between vasopressin administration in patients with septic shock and increased occurrence of digital ischemia [65, 66]. Another explanation may be the absence of hemodynamic profiling in the selection of patients exposed to vasopressin, while vasopressin is a pure vasopressor, unlike norepinephrine which is an inopressor [24]. Therefore, vasopressin may be more effective in improving the trajectory of the SOFA score, renal function, and organ perfusion in patients with hyperdynamic shock and a cardiac index > 3 L/min/m^2 [67].

Vasopressin deficiency

At the early phase of septic shock, blood vasopressin concentration increases [54, 68], while at the late phase of septic shock, up to one-third of patients may have vasopressin deficiency, which contributes to refractory septic shock [18, 68, 69] (Fig. 3). At comparable MAP levels, patients with septic shock exhibit a more significant vasopressin deficiency compared to healthy subjects and patients with cardiogenic shock. This is likely due to impaired baroreflex-mediated secretion [70]. Thus, vasopressin release in response to increased plasma osmolality and/or decreased blood pressure may be reduced in patients with septic shock, due to impaired baroreflex response caused by sepsis-related sympathetic dysfunction [71, 72]. Although half of septic-shock patients do not respond to hypertonic osmolar stimulation [73], the fact that responders and non-responders have similar blood osmolarity and blood sodium concentrations suggests that other mechanisms are involved in vasopressin deficiency.

The other pathophysiological hypotheses suggested to explain vasopressin deficiency include deficient sensing of stimulating signals, impaired vasopressin production capacity and downregulation of V1 receptors membrane expression [71, 73–76]. First, pituitary vasopressin stores are massively depleted within the first two hours of septic shock [77], as shown by the absence of spontaneous hypersignal in the posterior pituitary gland on T1-weighted MRI [75]. A study combining experiments on rats and post-mortem analysis in humans, suggests this depletion results from post-transcriptional regulation and altered transport to the hypothalamus's paraventricular and supraoptic nuclei parts [45]. Second, sepsis is associated with neuronal apoptosis in autonomous brain centers [76, 78]. Third, patients with septic shock exhibit both qualitative [74] and quantitative (cytokine-mediated downregulation) defects in V1 receptor [79].

Norepinephrine-sparing effect

Some pilot studies found that vasopressin administration in patients with septic shock requiring high doses of norepinephrine was associated with a decrease in norepinephrine dose [67, 80–83]. Morelli *et al.*. found that vasopressin administration (fixed dose at 0.04 U/min) decreased norepinephrine requirements at the end of the 6-hour study period [84]. Similarly, Patel *et al.*. found that vasopressin administration (titrated on MAP level up to 0.08 U/min) spared norepinephrine while preserving MAP and cardiac index [81].

The three aforementioned large trials (VASST, VANISH and VANCS) have shown that vasopressin administration spares norepinephrine use in patients with septic shock [60–62], which is an interesting strategy in terms of decatecholaminization. Nevertheless, the potential benefits of such a catecholamine-sparing strategy must be weighed against the potential ischemic effects of vasopressin and confirmed by more patient-centered outcomes.

Vasopressin and cardiac function

Although vasopressin is a pure vasoconstrictor, the administration of vasopressin in patients with septic shock who are already receiving ≥ 0.5 µg/kg/min of norepinephrine may induce a significant increase in cardiac output, stroke volume, left ventricular stroke work index and a significant decrease in heart rate compared to patients who receive norepinephrine alone [80]. This unexpected improvement in myocardial performance at first glance may be explained by (i) a reduction in norepinephrine-induced cardiotoxicity and arrhythmias induced by norepinephrine, (ii) an attenuation of nitric oxide production, (iii) an increase in myocardial intracellular calcium mediated by V1 receptor activation and (iv), an increase in myocardial blood flow [80]. Conversely, some patients are at risk of a vasopressin-induced decrease in cardiac output alongside a dose-dependent increase in systemic arterial pressure [85], as well as vasopressin-induced coronary vasoconstriction [86]. Vasopressin may therefore induce a marked increase in left ventricular afterload, leading to ventriculo-arterial uncoupling and decreasing cardiac output and venous oxygen saturation [87]. Finally, the decrease in norepinephrine doses may also lead to decreased β-adrenergic stimulation, which contributes to the decrease in cardiac output [88]. It is therefore crucial to carefully check left ventricular systolic function before administering

vasopressin [89] and to reassess cardiac output after the introduction of vasopressin [90].

The VASST, VANISH and VANCS II trials found no difference in the incidence of life-threatening cardiac arrhythmia between norepinephrine and vasopressin groups [60–62]. Moreover, an aggregate data meta-analysis including 17 studies and 1,462 patients showed a reduced risk of atrial fibrillation in the vasopressin group compared to the norepinephrine group (OR 0.77 (0.67–0.88), $p < 0.001$, low heterogeneity, I^2: 1%) [65]. It should be noted that this effect was mainly driven by the VANCS trial (accounting for 75% of the weight) [91] which was the only trial to find a significantly reduced risk of atrial fibrillation. This trial included both patients with septic shock and post-cardiac surgery patients [91]. A post hoc analysis of the VASST trial found no difference in electrocardiogram findings or troponin levels [92].

Vasopressin may also reduce myocardial injury. Sepsis-induced cardiomyopathy occurs in 20–65% of patients with septic shock and is associated with severe cardiac dysfunction in 24% of cases [93]. Compared to norepinephrine alone, the combination of vasopressin and norepinephrine in a porcine model of fecal peritonitis decreased heart rate and cardiac output as well as troponin I blood levels [94], similarly to angiotensin II [95, 96]. Therefore, vasopressin may be a promising alternative for reducing catecholamine exposure in patients with sepsis-induced cardiomyopathy, despite evidence suggesting that vasopressin use does not reduce histological lesions in this condition [40].

Ultimately, no definitive conclusions can be drawn about vasopressin impact on cardiac function in patients with septic shock.

Vasopressin and renal function

Vasopressin may also have a beneficial effect on renal perfusion and therefore on renal function [81], related to V1-mediated efferent arteriolar vasoconstriction which increases the intra-glomerular pressure [97] and V2-mediated afferent arteriolar vasodilation [98]. The effects of vasopressin administration on renal outcomes in patients with septic shock in the different randomized controlled trials are summarized in Table 2. Unfortunately, not all the potential beneficial effects of vasopressin on improving renal perfusion translate into relevant clinical outcomes. A small randomized, double-blind, controlled trial of 24 patients with septic shock requiring high doses of vasopressors showed that vasopressin administration, compared to norepinephrine, was associated with a twofold increase in urinary output and an increase in creatinine clearance, with no effect on natriuresis or urine osmolarity [81]. The VANCS II trial found

Table 2 Randomized controlled trials assessing the effects of vasopressin on renal outcomes in patients with septic shock

Trial	Design	Sample size	Intervention group	Control group	Primary endpoint	Norepinephrine dose at randomization	Initiation time from diagnosis of septic shock	Use of steroids	Main results on renal outcomes
Patel 2002 [81]	Double Blind Single Center	24	AVP 0.01–0.08 U/min	NE 2–16 µg/min-	NE dose at 4 h while maintaining MAP > 65mmHg	20 µg/min (NE group) 25 µg/mn (AVP group)	No data	No data	Increased creatinine Increased clearance Increased urine output
Lauzier 2006 [67]	Open Label Multicenter	23	AVP 0.04–0.20 U/min	NE 0.1–2.8 µg/kg/min	Hemodynamic parameters and SOFA score at 48 h	0.20 µg/kg/mn (NE group) 0.18 µg/kg/mn (AVP group)	< 12 h	Yes	Improvement in24-hour creatinine clearance
VANISH 2016 [61]	Double Blind Multicenter	409	AVP 0.06 U/min	NE titrated up to 12 µg/min	Kidney failure-free days	0.16 µg/kg/min	3.5 h	Yes	No difference in kidney failure-free days Less use of RRT
REPERFUSE 2024 [170]	Single Center	45	vasopressin or angiotensin-II	NE for MAP > 65 mmHg	Renal cortical mean transit time at 24 h	> 0.1 µg/kg/min	In progress	Yes	In progress

AVP: Arginine vasopressin; NE: Norepinephrine; MAP: Mean arterial pressure; AKI: Acute kidney injury; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment; U/min: Units per minute; µg/min: Micrograms per minute; µg/kg/min: Micrograms per kilogram per minute

that vasopressin administration had no renal protective effect and did not reduce the need for renal replacement therapy (RRT). Although the VANISH trial found no difference regarding the primary outcome of kidney injury-free days, defined as days alive and free of kidney injury according to stage 3 of the Acute Kidney Injury Network (AKIN) classification, vasopressin administration, compared to norepinephrine, was associated with a reduction in the need for RRT (25.4% vs. 35.3%, absolute difference of −9.9 (95% CI −19.3 to −0.6), $p < 0.007$) [61]. This positive effect of vasopressin on the need for RRT was confirmed in *a post-hoc* analysis of the VASST trial (37.7% vs.17.0%, $p = 0.02$) [99]. However, the conclusions of the post-hoc analysis of the VASST trial were flawed for many reasons. First, there was a lack of standardized criteria to initiate RRT. Second, the observed difference was mostly due to the difference in the non-survivor group. Third, this supposed beneficial effect was only observed in the subgroup of patients classified "at risk" according to the RIFLE classification and not in the other patients, including those who did not suffer from chronic kidney disease at inclusion. Two meta-analyses assessed the effects of vasopressin administration on renal outcomes. The first one found a reduction in the need for RRT, but the results of this meta-analysis were flawed by significant heterogeneity ($I^2 = 70\%$) with no demonstrated impact on the risk of acute kidney injury [65]. The second one found that the need for RRT was reduced with vasopressin administration, but this result was not robust to sensitivity analyses and interaction tests were non-significant in the predefined subgroups [63].

Vasopressin and microcirculation

Microcirculation abnormalities have been found in patients with septic shock and appeared to be related to patients' outcomes [100]. In a pig model of mesenteric ischemia, vasopressin was associated with decreased endothelin-1 expression and increased capillary density [101]. Therefore, it was first suggested that vasopressin may induce less vasoconstriction than norepinephrine in the mesenteric, coronary, and cerebral circulations. Consequently, vasopressin was initially proposed as a potential therapeutic agent for managing non-occlusive mesenteric ischemia in the specific context of refractory vasoplegia induced by cardiopulmonary bypass [102]. Nevertheless, the vasopressin-induced mesenteric vasoconstriction [103] can also lead to mesenteric ischemia [104, 105].

In patients with septic shock, vasopressin use resulted in an increase in gastrointestinal perfusion and splanchnic blood flow while gastric mucosal irrigation was decreased [80, 106]. In a randomized trial including 24 patients with septic shock that required high-dose vasopressor support, short-term vasopressin administration improved gut microcirculation compared to norepinephrine [81]. In another randomized trial including 60 patients with septic shock receiving norepinephrine to maintain MAP between 65 and 75 mmHg, vasopressin administration as a second-line vasopressor did not improve sublingual microcirculation compared to terlipressin or placebo [84]. The effects of vasopressin on microcirculation remain therefore inconsistent, probably because the microcirculatory beds studied differ from one study to another as do the vasopressin doses. Overall, these data do not allow any definitive conclusions to be drawn about the impact of vasopressin use on microcirculation in patients with septic shock.

Gaps in knowledge

The SSC guidelines suggest initiating vasopressin as second-line vasopressor in patients who require doses of norepinephrine base > 0.25–0.50 µg/kg/min [5], after excluding persistent hypovolemia and cardiac dysfunction [69, 90]. However, several issues remain to be clarified and represent future areas of research to optimize and personalize the use of vasopressin and to better identify the subgroups of patients likely to benefit most from its use (Fig. 4).

How to identify patients who could benefit from vasopressin?

Only a third of patients with septic shock experience vasopressin deficiency and responsiveness to vasopressin is correlated with survival [107]. Identifying patients likely to benefit from vasopressin supplementation is therefore a crucial issue, which remains a challenge to this day, even with machine learning algorithms [108]. Measuring blood vasopressin concentration remains technically challenging because of its short half-life [109], but copeptin, secreted in quantities equimolar to vasopressin, could be a surrogate marker [110]. Dynamic tests, such as hypertonic saline infusion (5% hypertonic saline at 0.06mL/kg/min over two hours *via* a central venous catheter), could assess the osmoregulatory response and help distinguish patients with septic shock with or without increase in blood vasopressin concentration in relation to an increase in blood sodium concentration [73]. The hypertonic saline-stimulated copeptin test may be more effective than the arginine stimulation test in diagnosing vasopressin deficiency [111], but it remains unclear whether static or dynamic tests of the vasopressin axis will help identify patients with septic shock and vasopressin deficiency.

An alternative approach would be to sequence patients' single nucleotide polymorphisms to determine which vasopressor would be most appropriate, given the polymorphic variability of the adrenergic or vasopressin receptors. However, the delay in direct sequencing

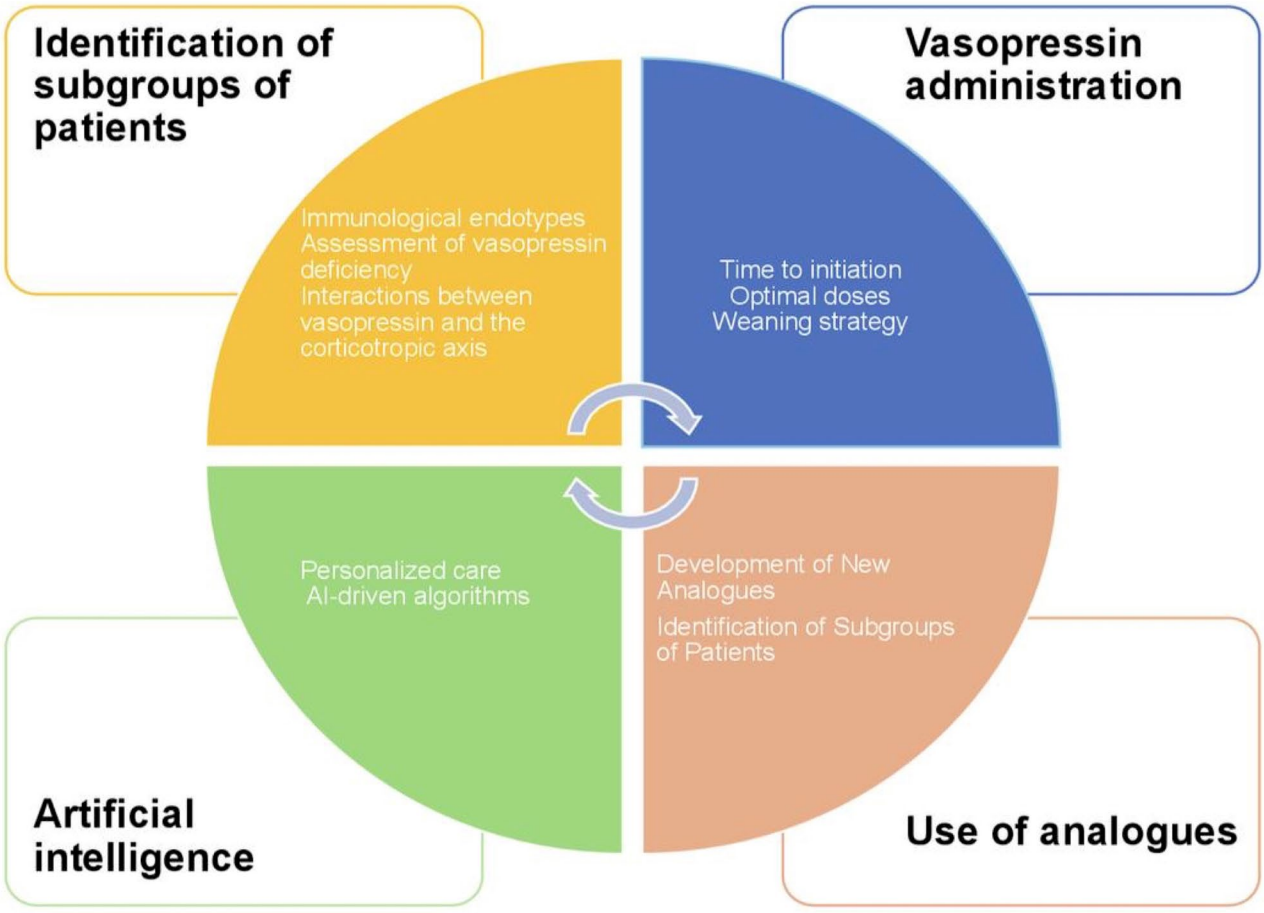

Fig. 4 Future areas of research on the use of vasopressin and its analogues in patients with septic shock. First, a better identification of subgroups of patients likely to benefit most from vasopressin administration. Second, the management of vasopressin administration (time to initiation, optimal doses, weaning strategy). Third, the development of artificial intelligence (AI)-driven algorithms to personalize strategies and improve patient outcomes. Fourth, to better define the place of the analogues in the management of patients with septic shock

prevents this approach from being used in routine care [112].

When vasopressin should be started?

The timing of vasopressin administration in patients with septic shock remains a complex and unresolved issue, which must take into account the balance between its potential benefits and the adverse effects expected when using a second-line vasopressor, such as increased left ventricular afterload, cardiac arrhythmias or impairment of regional perfusion [113]. In the near future, artificial intelligence-driven optimization of vasopressin use could also be a crucial tool for personalizing strategies and thus improving patient outcomes and mortality.

Administration based on the norepinephrine dose

First, before considering a predefined fixed dose of norepinephrine to initiate vasopressin, physicians should be aware that different formulations of norepinephrine are used worldwide with norepinephrine base in the United States and mainly norepinephrine tartrate in Europe. Importantly, norepinephrine base and norepinephrine tartrate are not equivalent, with norepinephrine base being twice as potent as norepinephrine tartrate (2 mg norepinephrine tartrate = 1 mg norepinephrine base) [114]. Given the different norepinephrine formulations that exist, it is difficult to make comparisons across different regions and standardizing the definition of refractory septic shock and practices remains a challenge [24]. In this regard, a single norepinephrine formulation has recently been recommended [115] to ensure consistency across international studies and clinical settings. Second, the median norepinephrine dose at vasopressin initiation (0.16 µg/kg/min in the VANISH trial vs. 0.55 µg/kg/min in the VASST trial) and the maximum dose of vasopressin (0.06U/min in the VANISH trial vs. 0.03U/min in the VASST trial) differed between trials [60, 61] (Table 2), making it difficult to clearly identify a predefined dose of norepinephrine for vasopressin initiation. However, the efficacy of vasopressin may depend on the dose of

norepinephrine at which it is initiated. A subgroup analysis of the VASST trial showed potential efficacy of vasopressin on mortality in the less severe patients requiring norepinephrine doses < 15 µg/min [60]. Retrospective studies confirm that initiating vasopressin at low-dose of norepinephrine was associated with an improved mortality in patients with septic shock [116, 117]. Sacha et *al.* found a 20.7% increase in in-hospital mortality for every 10 µg/min increase in norepinephrine-equivalent dose at the time of vasopressin administration, but there was no longer any association between mortality and the norepinephrine dose when the latter exceeded 60 µg/min [117]. This association between mortality and the norepinephrine dose at the time of vasopressin administration was found irrespective of the blood lactate concentration of patients [118]. Initiation of vasopressin at low-dose of norepinephrine was also associated with longer norepinephrine- mechanical ventilation- and RRT-free days [116], a lower fluid balance and a shorter time to shock resolution [119]. There appears to be an inconsistent association between the dose of catecholamine at the time of vasopressin initiation and the response to vasopressin. In a retrospective study including 938 patients with septic shock receiving a fixed dose of vasopressin for at least six hours, Sacha *et al.* found that the norepinephrine equivalent dose at the time of vasopressin administration was not associated with the response to vasopressin, defined as a decrease in catecholamine dose and MAP ≥ 65 mmHg within six hours of the start of vasopressin administration [120]. Conversely, a prospective multicenter observational study including 200 patients with septic shock found an association between the response to vasopressin and the dose of norepinephrine base at the time of vasopressin initiation when the latter exceeded 0.3 µg/kg/min [121].

Administration based on time from onset of septic shock

As with the norepinephrine dose, the time to initiation of vasopressin from onset of septic shock differed between trials (3.5hours in the VANISH trial vs. 12hours in the VASST trial) [60, 61] (Table 2), so it is also difficult to clearly identify the right time to initiate vasopressin in patients with septic shock. Conflicting results have been reported regarding early administration of vasopressin (defined as < 3 hours to 72 hours after the onset of septic shock) with a negative [122, 123] or positive [124, 125] association with mortality in patients with septic shock. In their large retrospective study, Sacha et *al.* found no association between time from onset of septic shock to vasopressin initiation and mortality [117]. Besides mortality, early initiation of vasopressin has been associated with faster achievement of hemodynamic goals [124, 126], faster correction of organ dysfunction [127], reduced incidence of new onset cardiac arrhythmias [128, 129], shorter duration of septic shock [125, 128] or shorter ICU length of stay [125, 128]. Heterogeneity in these results may be partly explained by the heterogeneity in the use of vasopressin and the definition of early vasopressin administration between the different studies [118].Meta-analyses found that vasopressin administration within the first six hours from the onset of septic shock was associated with a reduced need for RRT [64, 130] and a shorter duration of vasopressor use [130], but not with a decreased mortality [64, 130]. A very recent meta-analysis including 11 studies and 6,661 patients with septic shock suggested that "early" vasopressor initiation (within one to three hours after the onset of septic shock) was associated with lower short-term mortality than "late" vasopressor initiation (after three hours after the onset of septic shock) in both cohort studies (OR 0.40, 95% CI 0.21–0.76) and randomized trials (OR 0.49, 95% CI 0.25–0.96) [131]. Conversely, no association was found between "extremely early" administration of vasopressors (within the first hour after the onset of septic shock) and short-term mortality (OR 0.61, 95% CI 0.20–1.89; I^2 = 91%)" [131]. Finally, a target trial emulation including 3,105 patients confirmed that patients with septic shock might benefit from early (≤ 6 h) vasopressin administration with lower 30-day mortality [132].

To summarize, neither a predefined fixed dose of norepinephrine, nor a predefined time from onset of septic shock appears to be sufficiently reliable markers to guide vasopressin administration in patients with septic shock. It should be kept in mind that the distinction between "early" vs. "late" use of second-line vasopressor depends on the disease course rather than on time itself. In addition, introducing vasopressin at a predefined fixed dose of norepinephrine is not synonymous of early administration, as this predefined fixed dose of norepinephrine may be reached at different times after the onset of septic shock [133]. It is therefore probably more relevant to consider early administration of vasopressin in terms of vasopressor load [134, 135], as the longer the duration of exposure to high norepinephrine doses, the poorer the prognosis for patients. Very recently, the OVISS study using artificial intelligence-driven optimization of vasopressin found that in patients with septic shock, a more frequent use of vasopressin, in less severe patients, with an earlier administration of vasopressin after shock onset (4 [1–8] hours) at lower dose of norepinephrine base (0.20[0.08–0.45] µg/kg/min) and lower blood lactate concentration (2.5[1.7–4.9] mmol/L) was associated with a decreased mortality [136]. An ongoing randomized trial comparing the effects on 28-day mortality of the addition of vasopressin at two doses of norepinephrine base (0.1 and 0.4 µg/kg/min) in patients with septic shock patients will add additional results in a near future (NCT06217562).

Administration based on the occurrence of acidemia

In a retrospective multicenter study, the hemodynamic response to vasopressin decreased and the norepinephrine doses increased as pH decreased, even after adjustment for patient severity and blood lactate concentration [137]. A *post-hoc* analysis of the VASST trial also demonstrated a significant reduction in 28-day and 90-day mortality rates with vasopressin administration compared to norepinephrine administration only in patients with blood lactate concentration ≤ 2mmol/L [138]. Finally, Sacha et *al.* found that higher blood lactate concentration at the time of vasopressin initiation was associated with higher mortality in patients with septic shock [117]. This decreased hemodynamic response to vasopressin in the context of acidemia probably reflects a multifactorial process involving reduced V1 receptor affinity, smooth muscle hyperpolarization mediated by K-ATP channel, intracellular calcium sequestration, increased nitric oxyde-driven vasodilation, and negative inotropic effect especially in patients with low cardiac output [137]. All these results suggest that vasopressin should be initiated before the occurrence of acidemia, thus probably early in the management of patients with septic shock.

How vasopressin should be used?

To date, the only available vasopressin protocols are those described in the three large randomized trials [60–62]. However, as each trial used its own protocol, there are currently as many protocols for the use of vasopressin as there are ICUs. For instance, the most common vasopressin doses used in United States range from 0.02 to 0.04 U/min. In our ICU, we adhere to the VANISH protocol [61] protocol, titrating vasopressin dose from 0.02 to 0.06 U/min. The question of whether the vasopressin dose should be fixed or titrated remains open, as does the question of the maximum dose. A small observational study including 92 patients with septic shock requiring ≥ 0.2 µg/kg/min noradrenaline showed that the administration of a bolus of vasopressin at 1U, followed by continuous infusion at 1 U/h, was safe and resulted in a faster rise in arterial pressures [139]. Moreover, changes in MAP induced by the vasopressin loading could reliably predict changes in catecholamine index after continuous vasopressin infusion [139]. Whatever the doses of vasopressin considered, it appears safe to use vasopressin with caution in patients with a medical history of ischemic disease.

How vasopressin should be weaned?

Seven retrospective studies found that vasopressin should be tapered after norepinephrine to avoid arterial hypotension, while the single small, randomized trial found opposite results [140]. However, there was no impact of the occurrence of arterial hypotension and mortality [140]. The very recent randomized trial RENOVA including 91 patients receiving norepinephrine and vasopressin found a trend towards a higher incidence of arterial hypotension in the first 24 h after vasopressor reduction (43.6% vs. 25.6%, $p = 0.15$), when weaning was initiated with norepinephrine [141].

Whatever weaning strategy is considered, physicians should keep in mind that vasopressin is a pure vasopressor, unlike norepinephrine which is an inopressor [24]. Therefore, weaning from norepinephrine results in a loss of its inotropic activity and some patients may experience or unmask cardiac dysfunction when given vasopressin alone, due to increased left ventricular afterload.

Should vasopressin be used in combination with corticosteroids?

Although an interaction between vasopressin and steroids has been found in experimental sepsis models [142], the potential clinical significance of this interaction in patients with septic shock remains to be fully elucidated [143, 144]. Vasopressin administration decreases the mortality rate only in patients with septic shock who receive both vasopressin and corticosteroids [145] and patients who receive the combination of vasopressin and hydrocortisone within the first 12 h after the onset of septic shock have a shorter time to resolution of shock [146]. Overall, these results suggest a synergistic interaction between vasopressin and corticosteroids administration in patients with septic shock. However, such an interaction deserves to be studied more in-depth, as it has been shown that plasma vasopressin concentrations may be significantly higher in patients with adrenal dysfunction than in patients with an appropriate cortisol response to ACTH [54].

Vasopressin may also have immunological effects, as the use of vasopressin has been associated with a decrease in pro-inflammatory cytokine levels in patients with septic shock, although this association did not persist after adjustment for corticosteroid use or shock severity [147]. This immunological effect of vasopressin has also been suggested in a *post-hoc* analysis of the VANISH trial, which found that the anti-cytokine effect of hydrocortisone was enhanced when it was combined with vasopressin or norepinephrine [148].

These hypotheses remain speculative and no interaction was found between vasopressin and hydrocortisone administration in the VANISH trial [61]. Furthermore, no interaction was found in a *post-hoc* analysis of the VANISH trial between the type of transcriptomic sepsis response signatures and the use of vasopressin or norepinephrine, while the transcriptomic sepsis response signature was associated with the response to corticosteroids [149]. A thorough evaluation of the interactions between vasopressin and the corticotropic axis could help to

identify which patients with septic shock would benefit most from vasopressin administration.

Even though the use of vasopressin was rare (1 patient out of 1,157) or unspecified in the two recent pivotal trials on the effects of corticosteroids in patients with septic shock [150, 151], we believe that the administration of vasopressin and corticosteroids should be considered in combination in patients with refractory septic shock, as both treatments have a norepinephrine-sparing effect and allow correction of factors that contribute to refractory septic shock [69].

Are there any non-adrenergic alternatives to vasopressin?

The SSC guidelines [5] suggest the use of angiotensin II in patients with septic shock, but the evidence is of very low-quality. In the ATHOS-3 trial, angiotensin II was compared to placebo as second-line vasopressor in patients with vasoplegic shock (80% of whom had septic shock) who required norepinephrine doses > 0.2 µg/kg/min for > 6 h [152]. Angiotensin II significantly increased MAP without increasing the doses of norepinephrine in 70% of patients, compared to the placebo group. No effect on 28-day mortality was found, but the trial was not designed to detect this [152]. However, as 70% of patients in the ATHOS-3 trial [152] and in the post hoc analysis [153] had received vasopressin prior to randomization, it is not possible to draw any valid about the potential synergistic effect of combining vasopressin and angiotensin II in patients with septic shock.

In a multicenter retrospective cohort study, patients who received vasopressin were more likely to respond to angiotensin II administration (OR 6.05, 95% CI 1.98–18.6; $p = 0.002$). Nevertheless, the administration of vasopressin alongside angiotensin II was not associated with 30-day mortality. Furthermore, there was no difference in the requirement for continuous RRT or the incidence of acute kidney injury stages 2 or 3 between responders and non-responders to angiotensin II [154].

A meta-analysis of randomized trials showed that using non-adrenergic vasopressors including vasopressin, terlipressin, selepressin, angiotensin II, methylene blue, and hydroxocobalamin in patients with septic shock was associated with a lower mortality rate. However, none of the individual non-adrenergic vasopressors showed significant survival benefits [155].

From a physiological point of view, we believe that it could make sense to adapt vasopressor therapy to the biological profile of patients with septic shock [112, 156]. Therefore, rather than a stepwise approach, a physiologically guided vasopressor approach may be more appropriate [157]. Such an early multimodal vasopressor therapy approach would allow a combination of first-line vasopressors to be administered to patients with septic shock, targeting the different systems involved in cardiovascular homeostasis.

Is there still a place for analogues in patients with septic shock?

There are two synthetic analogues of vasopressin: terlipressin and selepressin. Terlipressin is a prodrug that is cleaved into vasopressin by endothelial peptidases. Terlipressin has a longer half-life than vasopressin and a higher affinity for V1 than for V2. Selepressin is a more recent synthetic analogue and a pure V1 agonist. Thus, both have a more marked vasopressor activity than vasopressin [18]. Pivotal trials on the use of analogues in patients with septic shock are summarized in Table 3.

No adverse ischemic effects were observed in these trials [158–160]. The largest randomized, multicenter, double-blind, controlled trial included 617 patients with septic shock and terlipressin was compared to norepinephrine as first-line vasopressor [161]. There was no difference in the 28-day mortality rate, number of vasopressor-free days, or change in SOFA scores on Day 7, so the trial was stopped for futility. Importantly, the proportion of patients with digital ischemia was higher in the terlipressin group than in the norepinephrine group (13% vs. 0.35%, $p < 0.0001$) [161]. A meta-analysis confirmed the increased risk of peripheral ischemia with the use of terlipressin, and more surprisingly, also found a reduction in mortality, but only in patients > 60 years of age [162]. Like vasopressin, terlipressin induces bradycardia and reduces cardiac output by increasing systemic vascular resistance, as founded in a scoping review of physiological studies [163].

Currently, the SSC guidelines weakly suggest against using terlipressin in patients with septic shock [5]. Nevertheless, specific subgroups of patients, such as patients with cirrhosis may benefit more from the use of terlipressin as a vasopressor [163, 164], as terlipressin is also recommended for the treatment of variceal bleeding.

Only two randomized trials assessed the effects of selepressin in patients with septic shock. In a phase 2 A trial, selepressin use had a norepinephrine-sparing effect, improved fluid balance and shortened the duration of mechanical ventilation [165]. The second trial was stopped for futility after including 828 patients. There were no significant differences between groups regarding the primary outcome (ventilator-free days and vasopressor-free days within 30 days) and key secondary outcomes (90-day mortality rate, RRT-free days and ICU-free days). There was also no difference between groups in terms of ischemic effects [166]. To date, selepressin is no longer marketed.

Table 3 Randomized controlled trials assessing the effects of analogues in patients with septic shock

Trial	Design	Sample size	Intervention group	Control group	Primary endpoint	Norepinephrine dose at randomization	Initiation time from diagnosis of septic shock	Use of steroids	Main results
Albanèse 2005 [171]	Open Label Single Center	20	Terlipressin bolus 1 mg, Second bolus if MAP < 65mmHg after 20 min	NE for MAP 65–75 mmHg	Hemodynamic variables, oxygen consumption, urine output, creatinine clearance, and blood lactate concentration.	1.7 µg/kg/min	No data	No	Decrease in cardiac index Increase in urine output Increase in creatinine clearance
DOBU-PRESS 2008 [160]	Open Label Single Center	59	Terlipressin bolus (1 mg) + dobutamine + norepinephrine OR Terlipressin bolus (1 mg) + norepinephrine	NE for MAP > 70mmHg	Hemodynamics and catecholamine doses at 24 h	> 0.9 µg/kg/min	No data	Yes	Norepinephrine sparing effect No effect on mortality
TERLIVAP 2009 [158]	Open Label Single Center	45	Terlipressin 1.3 µg/kg/h	AVP 0.03 U/min + NE 15 µg/min	Reduction of NE doses	No	No data	Yes	No difference in systemic or regional hemodynamics between groups
Svoboda 2012 [159]	Open Label Single Center	30	Terlipressin 4 mg/24 h for 72 h + Open label NE	Open label NE	Norepinephrine doses + 28- and 90-day mortality	> 0.6 µg/kg/min	> 24 h	No data	No difference in 28- or 90-day mortality between groups
Choudhury 2017 [164]	Open Label Single Center	84	Terlipressin 1.3–5.2 µg/min over 24 h	NE 7.5–60 µg/min	MAP of > 65mmHg for 48 h	No data	No data	No data	Prevention of variceal bleeding Improvement in survival at 48 h
Russel 2017 [165]	Double Blind Multicenter	53	Selepressin 1.25, 2.5, and 3.75 ng/kg/min until shock resolution (up to Day 7)	Open label NE	Stabilization of MAP	0.18 µg/kg/min	> 2 h and < 24 h	No data	Lower fluid balance Increased ventilation-free days No effect on mortality
Liu 2018 [161]	Double Blind Multicenter	526	Terlipressin: 20–160 µg/h	NE 4–30 µg/min	28-day mortality	0.47 µg/kg/min	No data	No data	No difference between groups in: ● 28-day mortality ● SOFA score at day 7 ● Number of vasopressor-free days More adverse effects
SEPSIS-ACT 2020 [166]	Double Blind Multicenter	868	Selepressin 1.7, 2.5, and 3.5 ng/kg/min	Open label NE	Ventilator- and vasopressor-free days at 30-day	0.25 µg/kg/min	< 12 h	Yes	No difference between groups in vasopressor- and ventilator-free days at 30-day No difference between groups in 30-day mortality.

Table 3 (continued)

Trial	Design	Sample size	Intervention group	Control group	Primary endpoint	Norepinephrine dose at randomization	Initiation time from diagnosis of septic shock	Use of steroids	Main results
Wang 2022 [172]	Open Label Single Center	22	terlipressin 1.3 µg/kg/hour for 24 h + standard of care	NE for MAP > 65mmHg	Peak sonographic signal intensity at 24 h after enrollment	No data	No data	No data	Higher peak renal ultrasound signal with terlipressin
Sahoo 2022 [173]	Open label Single Center	50	Terlipressin 0.02 µg/kg/min + NE 0.01–3 µg/kg/min	NE 0.01–3 µg/kg/min	Dose of NE for MAP > 65 mmHg 12 h after onset of terlipressin administration	0.20 µg/kg/min (NE group) 0.24 µg/kg/min (terlipressin group)	No data	No data	No difference between groups in: ● Mortality ● ICU length of stay Lower NE dose, blood lactate concentration and SOFA at 12 h

AVP: Arginine vasopressin; NE: Norepinephrine; µg/kg/min: Micrograms per kilogram per minute; µg/min: Micrograms per minute; µg/kg/h: Micrograms per kilogram per hour; ng/kg/min: Nanograms per kilogram per minute; ICU: Intensive care unit; SOFA: Sequential Organ Failure Assessment; MAP; Mean arterial pressure; PaO_2: Arterial oxygen pressure; FiO_2: Inspired fraction of oxygen

Conclusion

Because of the adverse effects of high doses of norepinephrine, it is currently suggested that vasopressin, a non-catecholaminergic vasopressor, be used as a second-line vasopressor in patients with septic shock requiring doses of norepinephrine base > 0.25–0.50 µg/kg/min, after excluding persistent hypovolemia and cardiac dysfunction. To date, the use of vasopressin has no beneficial effect on mortality and the reduction in the need for RRT and the risk of atrial fibrillation needs to be confirmed. Nevertheless, vasopressin use is associated with a norepinephrine-sparing effect, which is an interesting strategy in terms of decatecholaminization. Clinical use of vasopressin should balance hemodynamic goals and potential ischemic risks, especially in patients with impaired cardiac function or acidemia.

There are still several unresolved issues regarding the worldwide availability of vasopressin, the identification of subgroups of patients most likely to benefit from it and the management of its administration, including the timing of its initiation, the optimal dose and the weaning strategy. Patient selection and the timing of vasopressin administration remain particularly critical, and future approaches may be guided by biomarkers such as copeptin or dynamic tests to help personalize therapy. A better understanding of the interactions between vasopressin and corticosteroids is also needed. The results of an ESICM-endorsed survey on vasopressin use in patients with septic shock (PRESS Survey) will provide new insights into these issues and could be the first step in further studies.

Abbreviations

ACTH	Adrenocorticotropic Hormone
V1	Arginine Vasopressin Receptor 1
V2	Arginine Vasopressin Receptor 2
V3	Arginine Vasopressin Receptor 3
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
OR	Odds Ratio
RRT	Renal Replacement Therapy
SSC	Surviving Sepsis Campaign
SOFA	Sequential Organ Failure Assessment

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